

Original Report

## Seroprevalence of Parvovirus B19 Antibody in HIV-Positive Asymptomatic Persons

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### ABSTRACT

**Objective:** Parvovirus B19 is an important cause of chronic anemia in human immunodeficiency virus (HIV)-positive patients. Extensive seroprevalence studies for parvovirus B19 in HIV-positive individuals have not been carried out in the United States. The authors compared the seroprevalence for parvovirus B19 among patients with asymptomatic HIV infection and healthy blood donors.

**Methods:** The seroprevalence of IgG antibodies to VP-1, a parvovirus B19 structural protein, was determined using an indirect enzyme immunoassay (EIA) and a Western blot assay in 72 HIV-positive adults without prior opportunistic infection or acquired immunodeficiency syndrome (AIDS)-related malignancy and results were compared to those of 134 healthy blood donors.

**Results:** There was a significantly higher seroprevalence for parvovirus B19 in HIV-positive subjects (57/72, 79%) than in the controls (58/134, 43%) ( $P < 0.001$ ). Analysis by indirect EIA of the HIV-positive subjects 1 year later showed no significant change in seropositivity (48/70, 69%). For HIV-positive subjects, B19 seropositivity was not significantly related to age, sex, or CD4 count, but the parvovirus index did correlate with the total IgG level at both time points ( $P = 0.014$  at the first estimation and  $P = 0.045$  1 year later). Western blot analysis of IgG antibody to the VP-1 protein showed that 49 of 71 (69%) of the HIV-positive subjects were positive at the beginning of the study, and 50 of 71 (70%) were positive 1 year later.

**Conclusions:** These results suggest an increased seropositivity to parvovirus B19 among HIV-positive individuals compared to healthy controls.

**Key Words:** asymptomatic HIV-positive, B19 antibody, parvovirus seroprevalence

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Parvovirus B19 is an important human pathogen which causes asymptomatic childhood infection, the childhood exanthem erythema infectiosum (fifth disease), rheumatologic syndromes in adults, transient aplastic crisis in individuals with underlying hemolytic disorders, nonimmune hydrops fetalis, and chronic anemia in immunocompromised hosts.<sup>1–5</sup> Parvovirus B19 shows tropism for erythroid progenitor cells leading to a lytic infection resulting in marked reticulocytopenia. Infection in human immunodeficiency virus (HIV)-positive individuals leads to decreased red blood cell production due to their inability to clear the virus effectively, in turn leading to decreased red blood cell production.<sup>6</sup> However, in HIV-positive subjects, determination of the etiology of anemia is complicated by a variety of potential causes, including opportunistic infection, malignancy, drug toxicity, inappropriately low erythropoietin, or immune mediated mechanisms. The importance of identifying parvovirus as an etiologic factor in HIV-positive patients with anemia is emphasized by the fact that effective therapy is available. Intravenous immunoglobulin has been successfully used to treat parvovirus-induced anemia in HIV-positive patients.<sup>7</sup>

Human parvovirus is a small DNA virus that is encapsulated but lacks an envelope and has two capsid structural proteins: the VP-2 (58 kD) major protein and the VP-1 (83 kD) minor protein.<sup>8</sup> Humoral immunity with the production of neutralizing antibody is necessary to effectively clear the virus.<sup>9</sup> Antibody to the VP-1 minor capsid protein is produced after the first week of infection and forms the main antibody in individuals after recovery from acute infection.<sup>10</sup> Failure of this immune response results in failure to clear the virus.<sup>10</sup>

Seroprevalence studies in healthy blood donors show varying levels of B19 seropositivity, depending on geographic location. Rates of 73.7% in Rio de Janeiro, 38.4% in Munich, and 50% in Rochester, Minnesota, have been reported.<sup>11–13</sup> Data on the seroprevalence of antibody to parvovirus B19 in asymptomatic HIV-positive adults in

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the United States is limited. Several small seroprevalence studies in HIV-positive individuals have shown rates ranging from 27.5% to 64%.<sup>6,7,14,15</sup> Rates among HIV-positive hemophiliacs have been reported to be higher, at 91.7%.<sup>14</sup> In this study, the authors determined parvovirus B19 seroprevalence among HIV-positive individuals locally and compared this level to healthy blood donors from the same region. Samples were analyzed by ELISA and a confirmatory Western blot was performed on the HIV-positive individuals' samples to assess if the results obtained by ELISA were specific for parvovirus, in view of the non-specific elevations in immunoglobulin seen early in HIV infection.

## SUBJECTS AND METHODS

### Subjects

Retrospective analysis was performed on sera collected from 72 HIV-positive adults without prior opportunistic infection or AIDS-related malignancy enrolled in a separate study, after informed consent was obtained. The study was approved by the Institutional Review Boards of the Mayo Clinic, Park Nicollet Hospital, and the University of Minnesota VA Medical Center. Individuals were selected from HIV clinics in three urban centers in the region. All individuals were recently diagnosed with HIV infection in the absence of symptoms or anemia. The controls were 134 geographically matched healthy blood donors from urban centers whose sera was collected in a separate but chronologically concurrent study. There were slight differences between the control group and HIV-seropositive group with respect to the proportion of subjects from each urban center.

Serum specimens were collected from the 72 HIV-positive individuals after enrollment (T1) and a repeat collection was obtained 1 year later (T2) in 71 of these individuals and analyzed by enzyme immunoassay (EIA) for IgG to parvovirus B19 and by Western blot for IgM and IgG (one subject lost to follow-up, one subject did not have a Western blot IgG estimation at T1, one subject did not have EIA IgG estimation at T2). CD4 counts, measured by flow cytometry, and total IgG immunoglobulin levels, measured by nephelometry, also were obtained at the time of each sample. Each sample was analyzed by indirect EIA (MarDx Diagnostics, Inc., Carlsbad, CA) for IgG antibody to parvovirus B19 and by Western blot for IgM and IgG to VP-1 antigen (MarDx Diagnostics, Inc.). The control samples were analyzed by EIA for IgG to parvovirus B19.

### Indirect Enzyme Immunoassay for IgG

IgG antibody to parvovirus B19 was determined using an indirect EIA to the VP-1 antigen in a commercially available test kit (MarDx Diagnostics, Inc.). Samples were

analyzed in batch fashion using the same lot test kit. The performance of this kit previously has been described.<sup>13</sup> The results were compared to a high positive control, three low positive controls, and a negative control. A parvovirus index was calculated by dividing the optical density of the sample by the mean of the three low positive controls. The mean high positive control index was 3.046, the mean negative control was 0.546, and the mean of the low positive controls was 1.044. Results were reported as positive if the parvovirus index from duplicate measurements was greater than or equal to 1.0.

### Western Blot IgM and IgG

A Western blot for IgM and IgG was obtained on each sample from HIV-positive subjects (MarDx Diagnostics, Inc.). Western blots were read as negative, weakly positive, or strongly positive.

### Statistics

Statistical analysis was performed using Spearman's rank correlation to compare parvovirus index versus age, CD4 count, and immunoglobulin level. Seropositivity by indirect EIA at the two time points was compared using McNemar's test, and this technique was also used to compare seropositivity at each time point by indirect EIA with IgG Western blot. Pearson's chi-square test was used to compare differences in seropositivity by indirect EIA between subjects and controls.

## RESULTS

### Patient Population

The HIV-positive subjects ( $n = 72$ ) had a median age of 38.5 years (range, 24.5–72.0 y) at the beginning of the study; for the controls ( $n = 134$ ) the median age was 48.0 years (range, 21.0–79.0 y). Of the HIV-positive subjects, 66 of 72 (92%) were male compared with 67 of 134 (50%) for the controls. The mode of HIV acquisition in the HIV-positive subjects was homosexual contact in 56 of 72 (78%), heterosexual contact in 6 of 72 (8%), contaminated hemophiliac blood products in 5 of 72 (7%), intravenous drug abuse in 4 of 72 (6%), and contaminated blood transfusion in 3 of 72 (4%). Two subjects had two possible modes of infection. Fifty-six (78%) HIV-positive individuals were currently on anti-retroviral treatment: 30 (42%) AZT monotherapy, 4 (6%) ddI monotherapy, 3 (4%) ddC monotherapy, and 19 (26%) AZT and ddC combined; and 16 (22%) individuals were on no therapy. The median CD4 count at the time of the first sample collection (T1) was 280 cells/ $\mu$ L (range, 1–704 cells/ $\mu$ L), and at the time of the sample collected 12 months later (T2) was 200 cells/ $\mu$ L (range, 0–765 cells/ $\mu$ L). The corresponding figures for the total IgG levels at the same two points were T1, 1629 mg/dL (range, 852–3550 mg/dL) and T2,

**Table 1.** Results of Tests for Parvovirus B19 in Each Group

Group	Test	T1*	T2†
Controls:	EIA IgG	43% (58/134)‡	—
HIV-Positive:	EIA IgG	79% (57/72)‡	69% (48/70)
HIV-Positive:	WB IgG	69% (49/71)	70% (50/71)
HIV-Positive:	WB IgM	5.6% (4/72)	4.2% (3/71)

Seropositivity for each test in the different groups studied. EIA = enzyme immunoassay; WB = Western blot; \*T1 = baseline; †T2 = 1 year later;

‡P < 0.001.

1689 mg/dL (range, 551–3759 mg/dL) (normal range for IgG, 500–1200 mg/dL).

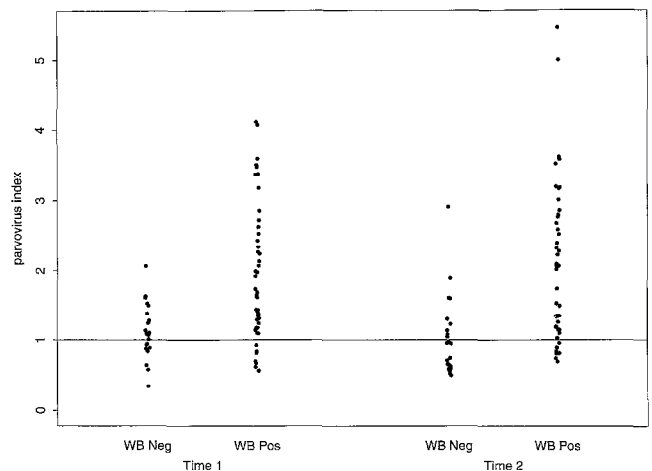
### Parvovirus IgG by Indirect Enzyme Immunoassay

In the control population, 58 of 134 (43%) subjects were seropositive compared to 57 of 72 (79%) in the HIV-positive subjects at T1 ( $P < 0.001$ ) (Table 1). The median parvovirus index in the controls was 0.836 (range, 0.100–5.936) compared to 1.3885 (range, 0.343–4.109) in the HIV-positive subjects at T1 ( $P = 0.008$ ). At T2, 48 of 70 (69%) of the HIV-positive subjects were seropositive (see Table 1), with a median parvovirus index of 1.280 (range, 0.501–5.936), which was not significantly different when compared to parvovirus index at T1. The agreement between values at T1 and T2 was 72.9% ( $P = 0.17$ ) (43 were positive at both times, 8 negative at both, 6 went from negative to positive, and 13 from positive to negative). There was no statistical association between age or sex and seropositivity in either controls or subjects. There was no association between parvovirus index and CD4 count at either point in time ( $P = 0.868$  at T1 and  $P = 0.740$  at T2). There was a trend toward seronegativity with lower total IgG immunoglobulin levels at T1 and T2, with the comparison of total IgG immunoglobulin level to parvovirus index at T1, ( $P = 0.0147$ ) and at T2, ( $P = 0.0454$ ), reaching statistical significance.

### Western Blot Analysis

By IgM Western blot 4 of 72 (5.6%) of HIV-positive subjects were found to be positive at T1 (see Table 1). Of these only one had a strong band, while the other three were weak. Two had positive IgG serologies, including the subject with a strong band, while two were IgG negative by indirect EIA. At T2, three subjects had weak IgM bands by Western blot, and all three had positive bands at T1 (one strong, two weak). The results of IgG serologies by indirect EIA for all four subjects with positive tests for IgM at T1 were the same at T2 as they had been at T1 (i.e., two positive and two negative); however, one of those with a negative result did switch Western blot IgG status from negative to positive. Of 64 sera tested from the control population, one sample had IgM class antibodies to parvovirus B19.

Western blot analysis for IgG showed 49 of 71 (69%) of HIV-positive subjects were positive by Western blot at



**Figure 1.** Comparison of results by IgG Western blot with the parvovirus index obtained by indirect EIA in the HIV-positive subjects shows the correlation between the tests. In particular, a number of specimens with low positive parvovirus index by indirect EIA were negative by Western blot. The line shows the cutoff for parvovirus index of 1.0 used to determine positive results by indirect EIA.

T1; 25 of 49 had strong bands (see Table 1). At T2, 50 of 71 (70%) of subjects had a positive Western blot result; 25 of 50 had strong bands. When these results were compared to the IgG results by indirect EIA they showed fair agreement, with 70.4% at T1 and 74.3% at T2 (Figure 1).

### DISCUSSION

The authors found that HIV-positive individuals have a higher seroprevalence of IgG antibodies (79%) to parvovirus B19 than healthy controls (43%), as determined by indirect EIA. Testing by IgG Western blot methods confirmed a similar rate (69%) in HIV-positive individuals. There was no significant change in seroprevalence by indirect EIA or IgG Western blot after 1 year in HIV-seropositive individuals. In addition, parvovirus index by indirect EIA was related to the total immunoglobulin level but not to the CD4 count.

The rate of seropositivity in HIV-positive adults (79%) compares with the rate of 60% described in a mixed population of 55 pediatric and adult HIV-positive cases in the United States and with a rate of 64% in 50 patients with AIDS compared with 85% in a control population also in the United States.<sup>6,7</sup> In Germany, parvovirus B19 seroprevalence rates were 27.5% in asymptomatic HIV-positive nonhemophiliac subjects, 91.7% in HIV-positive hemophiliacs, and 34.1% for a control population.<sup>14</sup> However in patients with chronic anemia seropositivity was lower; in a study of HIV-positive patients with chronic anemia, only 5 of 14 patients with CD4 counts less than

200 had IgG to parvovirus and all 5 were viremic by Southern blot analysis of polymerase chain reaction (PCR) product.<sup>15</sup> In another study, 0 of 7 subjects with chronic parvovirus infection, shown by detection of viral DNA and capsid protein, had detectable IgG to parvovirus.<sup>7</sup> In pediatric populations with AIDS, seropositivity rates tend to be lower: a rate of 40% was recorded in Italy and 27.5% in Romania.<sup>16</sup> Two studies designed to report the frequency of positive PCR tests for parvovirus DNA reported an incidence of IgG seropositivity of 7.6% and 81%, respectively.<sup>17,18</sup>

The design of the current study improves upon these previous reports, because the study group represents adult subjects tested soon after diagnosis of their HIV infection and is compared to a geographically local control group. This well-defined population is distinct from groups enrolled in previous studies in the United States, which have variously included both adult and pediatric populations or asymptomatic and symptomatic subjects, and have not always included a local control group. None of the previous studies compared seroprevalence results using different laboratory techniques or compared results to total IgG levels,<sup>6,7,14,15</sup> and only one study compared results to the CD4 count.<sup>18</sup>

The explanation of the increased seropositivity in HIV-positive individuals remains speculative. The attack rate of parvovirus B19 is high, approaching 50% in nonimmune adults. Spread via respiratory secretions facilitates community spread. Pentamidine use has been suggested as a possible method of airborne parvovirus B19 transmission if standard precautions of ventilatory control fail to inactivate the virus.<sup>19</sup> However, as the current study group was asymptomatic and recently diagnosed with HIV infection, this seems an unlikely explanation. Similarly, while blood products, especially clotting factors, may transmit parvovirus B19 infection, the low number of hemophiliacs or transfusion-related cases of HIV infection in this series, coupled with their asymptomatic state makes this an unlikely explanation.<sup>20,21</sup> To the authors' knowledge there have been no reports of sexual transmission of parvovirus B19. However, as the HIV-positive cohort contained 48% homosexual men, future studies should compare the seroprevalence in HIV seronegative homosexual men with that of HIV-seropositive homosexual men.

The increased seropositivity noted in this group of HIV-positive individuals suggests unidentified methods of transmission may play a role, and future studies should investigate the potential of sexual transmission. It is not known if exposure to parvovirus B19 results in detectable antibodies for life or if parvovirus B19 is capable of establishing latency. Relapse after treatment or primary infection has been described.<sup>22,23</sup> It is possible that asymptomatic reactivation of parvovirus B19 associated with decreased cell-mediated immunity leads to an elevation of parvovirus B19 antibodies, an effect that may be exacerbated by the production of nonneutralizing antibodies.

Although this study suggests parvovirus B19 infection may occur more frequently in HIV-seropositive individuals, the clinical relevance of this finding remains to be established. In contrast to findings in this study, clinical disease is rare in HIV-seropositive individuals. This may be because primary infection is rarely encountered, although findings in this study suggest prior infection is common and make this a less likely explanation. Alternatively, reactivation of parvovirus B19 from latency may be a rare event or the immune response to parvovirus B19 may be relatively well preserved in advanced HIV disease. Understanding the nature of parvovirus B19 immune determinants capable of inducing effective and long-lasting immunity is therefore important to vaccine research.

This study has limitations. The control population was not identical to the subjects. There was a difference in age with a higher median age in the controls, which should have biased the study in favor of finding no difference between groups. There also was a disparity in gender distribution, with the controls being evenly distributed with respect to gender and the subjects having a predominance of males, consistent with the demographics of HIV-positivity. Nevertheless these differences do not explain the differences in seropositivity, as the control group failed to show significant differences in seropositivity by age or sex. No evidence was found of a cohort effect in the controls or HIV-positive individuals. The makeup of the HIV-positive population differs from other HIV-positive populations, with a higher percentage of male homosexual patients and lower numbers of heterosexual, intravenous drug associated, female, inner city, or ethnic minority cases. Therefore, findings may not be applicable to all HIV populations.

Another potential limitation in this study was the ability to accurately diagnose parvovirus B19 seropositivity in cases with a parvovirus index just above the threshold of positivity. A parvovirus index of greater than 1.0 was used as the threshold for positivity. The kit is conventionally used, with the range 0.8-1.2 being reported as equivocal, and retesting being recommended. In this study, because there was only one sample at each time point, the cutoff was set at 1.0, with the understanding that, on an individual basis, the ability of the test kit to determine seropositivity might be exceeded; it was assumed that false positives would be balanced by false negatives. However, even if the results are reanalyzed to include equivocal, the conclusions remain unchanged. As Figure 1 demonstrates, samples with a parvovirus index of 1.0 to 2.0 frequently have a negative Western blot. In these cases a confirmatory positive Western blot may help confirm the presence of IgG antibodies. The presence of these samples with low positive parvovirus indices explains the lack of tight correlation between seropositivity by indirect EIA at each point of time and the comparison of seropositivity by indirect EIA and Western blot.

Most of the discordant results involved specimens with equivocal indirect EIA values, supporting this conclusion.

A potential concern is that the indirect EIA assay could just be measuring the effect of a nonspecific cross-reactive antibody. A strength of this study is that antibody to the same VP-1 antigen was measured by Western blot, which is less likely to detect cross-reactive antibodies and immune complexes. Discordant results between indirect EIA and Western blot have been suggested to be attributable to the production of antibody with a qualitative defect that does not bind to protein capsid epitopes.<sup>10</sup> This also might explain the lack of correlation between antibodies detected by indirect EIA and presence of virus neutralization.<sup>24</sup> The production of low levels of a qualitatively abnormal antibody would explain cases with a low positive parvovirus index and a negative Western blot IgG to parvovirus B19.

The association between parvovirus index and immunoglobulin level was as expected. However, the association of seropositivity with total IgG level did not reach statistical significance, suggesting that the hypergammaglobulinemia seen in HIV infection does not account for the higher seropositivity observed. A significant association of parvovirus seropositivity with CD4 count was not detected. These results suggest that, although HIV-positive individuals with decreased CD4 counts may have less effective immune response to T-lymphocyte dependent antigens,<sup>25</sup> they may still retain antibodies to antigens to which they have previously been exposed. Lastly, the fact that no significant change occurred in seropositivity over the 1-year period of observation is not surprising, as there would need to have been a large rate of parvovirus B19 antibody decline to be detected over a 1-year time period.

## CONCLUSIONS

Asymptomatic HIV-positive adults have a higher seroprevalence of parvovirus B19 IgG than do healthy blood donors. No evidence was found of a cross-reactive antibody, and the data suggest that HIV-positive individuals may be at higher risk of parvovirus B19 infection than healthy controls. Seropositivity to parvovirus B19 is not statistically correlated with total IgG levels, and previous studies show that patients with chronic anemia and parvoviremia have absent or low levels of these antibodies. The exact identity of these antibodies, their neutralizing capabilities, the mode of transmission, and the roles of reinfection and reactivation in parvovirus B19 infection of HIV-positive individuals all require further investigation.

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